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PTO/SB/21 (08-00)
Approved for use through 10/31/2002. OMB 0651-0031

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TRANSMITTAL FORM

(To be used for all correspondence after initial filing)

Application Number	09834,414
Filing Date	04/12/01
First Named Inventor	Sawada, Toyohiro, et. al.
Group Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	19941000410

Total Number of Pages in This Submission

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Date	May 17, 2001	

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PATENT
Attorney Docket No.: 019941-000410US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Toyohiro Sawada et al.

Application No.: 09/834,414

Filed: April 12, 2001

For: DRUG DELIVERY SYSTEM FOR
AVERTING PHARMACOKINETIC DRUG
INTERACTION AND METHOD THEREOF

Assistant Commissioner for Patents
Washington, D.C. 20231

Examiner: Unassigned

Art Unit: Unassigned

COMMUNICATION UNDER 37 CFR
§1.78(5)

Sir:

Applicants submit herewith a Certified Copy of an English translation of their Priority Document, i.e., U.S. Provisional Application No. 60/197,574, for the above-referenced application.

Respectfully submitted,

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October 5, 2000

CERTIFICATION OF TRANSLATION

This is to certify that the attached Japanese to English translation has been proofread and edited by a qualified professional translator competent in both languages, and is an accurate and complete rendering of the content of the original document to the best of our ability. The following document is included in this certification, Specification of "Drug Delivery System For Averting Pharmacokinetic Drug Interaction And Method Thereof".

A handwritten signature in cursive script, reading "Marlo R. Martin".

Marlo R. Martin, Ph.D.
Director

SPECIFICATION

DRUG DELIVERY SYSTEM FOR AVERTING PHARMACOKINETIC DRUG INTERACTION AND METHOD THEREOF

Technical Field

The present invention pertains to a novel means for averting undesirable pharmacokinetic (drug) interaction between multiple drugs (between drugs and foods) *in vivo* in humans, and uses as the means of aversion a drug delivery system with which the *in vivo* release time and/or the release site of the drug is controlled.

Background Art

Today drugs are rarely used singularly as a result of diversification of medicine and changes in patient phase with aging, and in many cases multiple drugs are administered simultaneously or at staggered administration times. In this case, interaction between drugs that are administered concomitantly sometimes occurs. Interaction between the drugs in question is classified as pharmacodynamic drug interaction, whereby there is a change in sensitivity, etc., to the drug at its site of action, and pharmacokinetic drug interaction, where there is a change in the *in vivo* kinetics of the drug. With respect to the former, interaction by concomitant use can be estimated if the clinical mode of action of the drugs is known, and the fact of the matter is that the actual results of concomitant therapy are improved using this same interaction. However, with respect to the latter, clinically, the *in vivo* kinetics of a drug is still unknown and even when it is known, unexpected results occur when drugs are combined ("Clinical Pharmacokinetics, Revised Version 2," Chapter VII: Drug Interaction, page 107, Ryuichi Kato, author, Nankodo Publishing).

Pharmacokinetic drug interaction almost always develops because the drugs themselves compete for one route (enzymes, carriers, etc.) when drugs that use the same routes in terms of drugs absorption, distribution, metabolism or excretion are used concomitantly.

This type of pharmacokinetic drug interaction is undesirable unless it is used for an additive action or synergism. The method has been adopted for averting concomitant use of drugs that interact with one another when a prescription is written by a physician or pharmacist whereby attention is drawn to "Drug Safety Data" presented by the Ministry of Health and Welfare and the column on precautions for concomitant use contained in the attached drug literature.

Moreover, the claim is presented in "Drug Prediction Manual," (Yasufumi Sawada, author; Yakugyo Jiho Publishers) that it is possible to avert interaction with an administration protocol whereby the administration time of concomitant drugs to a patient is staggered. However, the administration time is precisely specified and the protocol calls for administration of as much as 6 to 7 times/day with concomitant use of metal cation-containing antacids (magnesium, aluminum, etc.) and new quinolones

(norfloxacin, etc.), which were used as examples in this text, and in view of patient compliance, this protocol cannot realistically be used.

Consequently, even if from a pharmacological standpoint the drugs themselves realize excellent therapeutic results when used concomitantly, concomitant use has been averted in the past because of drug interaction and satisfactory therapeutic results could not be realized.

Moreover, since pharmacokinetic interaction with drugs is induced by some foods, pharmacists give instructions on how to take drugs explaining precautions when drugs are taken. However, this has become a source of reduced patient compliance.

Disclosure of the Invention

The inventors focused on the use of a drug delivery system for averting undesirable drug interaction, particularly pharmacokinetic drug interaction, and were successful at materialization of the same. They discovered that with respect to drug interaction that is produced as a result of the drugs themselves competing for one route (enzyme, carrier, etc.) when multiple drugs that use the same route in terms of drug absorption, distribution, metabolism or excretion are administered concomitantly, drug interaction at the route that is the problem can be averted by controlling the drug release time and/or release site with a drug delivery system. Furthermore, not only drug interaction between multiple drugs, but also interaction between drugs and foods, can be similarly averted.

Aversion of drug interaction as a purpose and use of the technology in question has not been specifically discussed in the technical field of drug delivery systems and furthermore, its future use has not been emphasized.

That is, the present invention pertains to a system for averting undesirable pharmacokinetic drug interaction between multiple drugs, which consists of controlling the *in vivo* release time and/or release site of 1 or multiple drugs. In particular, the present invention pertains to a system for averting undesirable drug interaction between multiple drugs that use the same route in terms of *in vivo* drug absorption, distribution, metabolism or excretion in humans, which consists of controlling the *in vivo* release time and/or release site of 1 or multiple drugs. The present invention is preferably a system for averting undesirable drug interaction between multiple drugs that are metabolized by the same molecular species of drug-metabolizing enzyme in humans, or between drugs and other drugs that inhibit the molecular species of drug-metabolizing enzymes that metabolize the same drugs, which consists of timed-release control of 1 drug or control of the site of release of 1 drug to the digestive tract. It is further preferred that the present invention is a system for averting undesirable drug interaction between multiple drugs metabolized by the drug metabolizing enzyme CYP3A4, or between drugs that are metabolized by CYP3A4 and other drugs that inhibit CYP3A4, which consists of timed release control or controlling release specifically in the lower digestive tract of 1 drug.

Moreover, the present invention pertains to the use of a drug delivery system for controlling the *in vivo* release time and/or release site of 1 or multiple drugs as a means of averting undesirable pharmacokinetic drug interaction between multiple drugs. In

particular, the present invention pertains to the use of a drug delivery system for controlling the *in vivo* release time and/or release site of 1 or multiple drugs as a means of averting undesirable drug interaction between multiple drugs that use the same route in terms of *in vivo* drug absorption, distribution, metabolism or excretion in humans. The present invention preferably is the use of a drug delivery system for timed-release control of 1 drug or control of the site of release of 1 drug to the digestive tract of 1 drug as a means of averting undesirable drug interaction between multiple drugs that are metabolized by the same molecular species of drug-metabolizing enzyme in humans, or between drugs and other drugs that inhibit the molecular species of drug-metabolizing enzymes that metabolize the same drugs. It is further preferred that the present invention is the use of a drug delivery system for timed-release control of 1 drug or control of release of 1 drug specifically to the lower digestive tract as a means of averting undesirable drug interaction between multiple drugs metabolized by the drug metabolizing enzyme CYP3A4, or between drugs that are metabolized by CYP3A4 and other drugs that inhibit CYP3A4.

Moreover, the present invention pertains to a method for averting undesirable pharmacokinetic drug interaction between multiple drugs by using a drug delivery system with which the *in vivo* release time and/or release site of 1 or multiple drugs is controlled. In particular, the present invention pertains to a method for averting undesirable drug interaction between multiple drugs that use the same route in terms of *in vivo* drug absorption, distribution, metabolism or excretion in humans by using a drug delivery system with which the *in vivo* release time and/or release site of 1 or multiple drugs is controlled. The present invention is preferably a method for averting undesirable drug interaction between multiple drugs that are metabolized by the same molecular species of drug-metabolizing enzyme in humans or between drugs and other drugs that inhibit the molecular species of drug metabolizing-enzymes that metabolize the same drugs by using a drug delivery system with which there is timed-release control of 1 drug or control of the site of release of 1 drug to the digestive tract. It is further preferred that the present invention is a method for averting undesirable drug interaction between multiple drugs metabolized by the drug metabolizing enzyme CYP3A4 or between drugs that are metabolized by CYP3A4 and other drugs that inhibit CYP3A4 by using a drug delivery system with which there is timed-release control of 1 drug or control of release of 1 drug specifically to the lower digestive tract.

The present invention further pertains to a drug preparation for averting undesirable pharmacokinetic drug interaction between multiple drugs with which the *in vivo* release time and/or release site of 1 or multiple drugs can be controlled. In particular, the present invention pertains to a drug preparation for averting undesirable drug interaction between multiple drugs that use the same route in terms of *in vivo* drug absorption, distribution, metabolism or excretion in humans with which the *in vivo* release time and/or release site of 1 or multiple drugs can be controlled. The present invention is preferably a drug preparation for averting undesirable drug interaction on the *in vivo* kinetics of concomitant drugs by drugs that inhibit *in vivo* metabolism of concomitant drugs in humans with which there is timed-release control of 1 drug or control of the site of release of 1 drug to the digestive tract. It is further preferred that the

present invention is a drug preparation for averting undesirable effects on the blood concentration of concomitant drugs by drugs that inhibit the *in vivo* metabolism of concomitant drugs by CYP3A4 in humans with which there is timed release control, or specifically control of release in the lower digestive tract of 1 drug.

Moreover, the present invention pertains to the use of a drug preparation with which the *in vivo* release time and/or release site of 1 or multiple drugs can be controlled in order to avert undesirable pharmacokinetic drug interaction between multiple drugs. In other words, the present invention pertains to a drug preparation with which the *in vivo* release time and/or release site of 1 or multiple drugs can be controlled in order to avert undesirable drug interaction between multiple drugs that use the same route in terms of *in vivo* drug absorption, distribution, metabolism or excretion in humans. The present invention is preferably the use of a drug preparation with which there is timed-release control of 1 drug or control of the site of release of 1 drug to the digestive tract of in order to avert undesirable drug interaction on the *in vivo* kinetics of concomitant drugs by drugs that inhibit the *in vivo* metabolism of concomitant drugs in humans. It is further preferred that the present invention is the use of a drug preparation with which there is timed-release control of 1 drug or control of release of 1 drug specifically to the lower digestive tract of in order to avert undesirable effects on the blood concentration of concomitant drugs by drugs that inhibit the *in vivo* metabolism of concomitant drugs by CYP3A4 in humans. Furthermore, the present invention pertains to a method for averting undesirable pharmacokinetic drug interaction between drugs and concomitant drugs by using a drug preparation with which the *in vivo* release time and/or release site of drugs is controlled. In particular, the present invention pertains to a method for averting undesirable drug interaction between drugs and concomitant drugs that use the same route in terms of *in vivo* drug absorption, distribution, metabolism or excretion in humans by using a drug delivery system with which the *in vivo* release time and/or release site of drugs is controlled. The present invention is preferably a method whereby a drug preparation is used with which timed-release control of drugs or control of the site of release of drugs to the digestive tract is possible in order to avert undesirable drug interaction on the *in vivo* kinetics of concomitant drugs by drugs that inhibit the *in vivo* metabolism of concomitant drugs by drug-metabolizing enzymes in humans. It is further preferred that the present invention is a method whereby a drug preparation is used with which timed-release control of drugs or control of release of drugs specifically to the lower digestive tract is possible in order to avert undesirable effects on the blood concentration of concomitant drugs by drugs that inhibit the *in vivo* metabolism of concomitant drugs by CYP3A4.

Moreover, the present invention pertains to a system for averting undesirable pharmacokinetic drug interaction between drugs and foods, which consists of controlling the *in vivo* release time and/or release site of drugs. In particular, the present invention pertains to a system for averting undesirable drug interaction between drugs and foods that use the same route in terms of *in vivo* drug absorption, distribution, metabolism or excretion in humans, which consists of controlling the *in vivo* release time and/or release site of drugs. The present invention is preferably a system for averting undesirable drug interaction between drugs and foods that are metabolized by the same molecular species

of drug-metabolizing enzyme in humans, or between drugs and food that inhibit the molecular species of drug metabolizing enzymes that metabolize the same drugs, which consists of timed-release control of drugs or control of the site of release of drugs to the digestive tract. It is further preferred that the present invention is a system for averting undesirable drug interaction between drugs and foods metabolized by the drug-metabolizing enzyme CYP3A4, or between drugs that are metabolized by CYP3A4 and foods that inhibit CYP3A4, which consists of timed release control or controlling release specifically in the lower digestive tract of drugs.

In addition, the present invention pertains to the use of a drug delivery system for controlling the *in vivo* release time and/or release site of drugs as a means of averting undesirable pharmacokinetic drug interaction between drugs and foods. In particular, the present invention pertains to the use of a drug delivery system for controlling the *in vivo* release time and/or release site of drugs as a means of averting undesirable drug interaction between drugs and food that use the same route in terms of *in vivo* drug absorption, distribution, metabolism or excretion in humans. The present invention preferably is the use of a drug delivery system for timed-release control of drugs or control of the site of release of drugs to the digestive tract as a means of averting undesirable drug interaction between drugs and foods that are metabolized by the same molecular species of drug metabolizing enzyme in humans or between drugs and foods that inhibit the molecular species of drug-metabolizing enzymes that metabolize the same drugs. It is further preferred that the present invention is the use of a drug delivery system for timed-release control of drugs or control of release of drugs specifically to the lower digestive tract of drugs as a means of averting undesirable drug interaction between drugs and foods metabolized by the drug metabolizing enzyme CYP3A4 or between drugs that are metabolized by CYP3A4 and foods that inhibit CYP3A4.

Furthermore, the present invention pertains to a method for averting undesirable pharmacokinetic drug interaction between drugs and foods by using a drug delivery system with which the *in vivo* release time and/or release site of drugs is controlled. In particular, the present invention pertains to a method for averting undesirable drug interaction between drugs and foods that use the same route in terms of *in vivo* drug absorption, distribution, metabolism or excretion in humans by using a drug delivery system with which the *in vivo* release time and/or release site of drugs is controlled. The present invention is preferably a method for averting undesirable drug interaction between drugs and foods that are metabolized by the same molecular species of drug-metabolizing enzyme in humans or between drugs and foods that inhibit the molecular species of drug metabolizing enzymes that metabolize the same drugs by using a drug delivery system with which there is timed-release control of drugs or control of the site of release of drugs to the digestive tract. It is further preferred that the present invention is a method for averting undesirable drug interaction between drugs and foods metabolized by the drug-metabolizing enzyme CYP3A4 or between drugs that are metabolized by CYP3A4 and foods that inhibit CYP3A4 by using a drug delivery system with which there is timed-release control of drugs or control of release of drugs specifically to the lower digestive tract.

Furthermore, the present invention pertains to a drug preparation for averting undesirable pharmacokinetic drug interaction between drugs and foods with which the *in vivo* release time and/or release site of drugs can be controlled. In particular, the present invention pertains to a drug preparation for averting undesirable drug interaction between drugs and foods that use the same route in terms of *in vivo* drug absorption, distribution, metabolism or excretion in humans with which the *in vivo* release time and/or release site of 1 or multiple drugs can be controlled. The present invention is preferably a drug preparation for averting undesirable drug interaction on the *in vivo* kinetics of drugs by foods that inhibit *in vivo* metabolism of drugs in humans with which there is timed-release control of drugs or control of the site of release of drugs to the digestive tract of drugs. It is further preferred that the present invention is an oral drug preparation for averting undesirable effects on the blood concentration of concomitant drugs by foods that inhibit the *in vivo* metabolism of drugs by CYP3A4 in humans with which there is timed-release control of drugs or control of release of drugs specifically to the lower digestive tract.

Moreover, the present invention pertains to the use of a drug preparation with which the *in vivo* release time and/or release site of drugs can be controlled in order to avert undesirable pharmacokinetic drug interaction between drugs and foods. In other words, the present invention pertains to a drug preparation with which the *in vivo* release time and/or release site of drugs can be controlled in order to avert undesirable drug interaction between drugs and foods that use the same route in terms of *in vivo* drug absorption, distribution, metabolism or excretion in humans. The present invention is preferably the use of a drug preparation, with which there is timed-release control of drugs or control of the site of release of drugs to the digestive tract in order to avert undesirable interaction on the *in vivo* kinetics of drugs by foods that inhibit the *in vivo* metabolism in humans of drugs by drug-metabolizing enzymes. It is further preferred that the present invention is the use of a drug preparation with which there is timed-release control of drugs or control of release of drugs specifically to the lower digestive tract in order to avert undesirable effects on the blood concentration of drugs by foods that inhibit *in vivo* metabolism of drugs in humans by drug-metabolizing enzymes.

Furthermore, the present invention pertains to a method for averting undesirable pharmacokinetic drug interaction between drugs and foods by using a drug preparation with which the *in vivo* release time and/or release site of drugs is controlled. In particular, the present invention pertains to a method for averting undesirable drug interaction between drugs and foods that use the same route in terms of *in vivo* drug absorption, distribution, metabolism or excretion in humans by using a drug preparation with which the *in vivo* release time and/or release site of drugs is controlled. The present invention is preferably a method for averting undesirable interaction on the *in vivo* kinetics of drugs by foods that inhibit the *in vivo* metabolism of drugs by drug-metabolizing enzymes in humans by using a drug delivery system with which there is timed-release control of drugs or control of the site of release of drugs to the digestive tract. It is further preferred that the present invention is a method for averting undesirable effects on the blood concentration of drugs by foods that inhibit *in vivo* metabolism of drugs in humans by CYP3A4.

The present invention will now be explained in further detail.

In the present invention the term drug interaction means pharmacokinetic drug interaction, in other words, drug interaction between multiple drugs that use the same route in terms of drug absorption, distribution, metabolism, or excretion. Specific interaction is discussed below:

(a) Interaction in terms of drug metabolism

Drugs are deactivated or converted to water-soluble metabolites that are readily excreted via the kidneys by the effects of drug-metabolizing enzymes in the liver. Cytochrome P450 (CYP) is said to be the most important drug-metabolizing enzyme. It is said that approximately 70% of pharmacokinetic drug interaction is around drug metabolism, and of this, 95% or more is interaction via CYP. Many molecular species of CYP exist, and those that play the most important role in drug metabolism are CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. The molecular species of CYP involved in drug metabolism is determined by the chemical structure of the drug. Moreover, the molecular species of CYP involved in metabolism varies with each site in the chemical structure, and there are also drugs that are metabolized by multiple molecular species of CYP.

When multiple drugs metabolized by the same molecular species of CYP compete for these metabolizing enzymes, the extent of competition varies with the affinity of the drug for the CYP, but it appears that metabolism is inhibited in some way. This results in drug interaction, such as an elevated blood concentrations, prolonged blood half-life, etc. Moreover, there are of course also drugs that are not metabolized, but have an inhibiting effect on specific molecular species of CYP.

Theophylline, caffeine, phenacetin, clomipramine, imipramine, fluvoxamine, zolpidem, clozapine, propranolol, propafenone, chlorzoxazone, tacrine, acetaminophen, ondasterone, verapamil, etc., are drugs that are metabolized by CYP1A2 and drugs that inhibit CYP1A2.

Diclofenac, naproxen, ibuprofen, piroxicam, flurbiprofen, indomethacin, phenytoin, carbamazepin, tolbutamide, glibenclamide, glipizide, glimepiride, warfarin, losartan, torsemide, dronabinol, tenoxicam, mefenamic acid, sulfafenazole, etc., are drugs that are metabolized by CYP2C9 and drugs that inhibit CYP2C9.

Mephenytoin, diazepam, phenytoin, phenobarbital, hexobarbital, mephobarbital, omeprazole, lansoprazole, proguanil, amitriptyline, clomipramine, imipramine, sitalopram, propranolol, thiridazine, carisoprodol, warfarin, nirvanol, etc., are drugs metabolized by CYP2C19 and drugs that inhibit CYP2C19.

Propafenone, flekainid, mexiletine, enkainid, spartein, N-propylazimalin*, metoprolol, timolol, pindolol, propranolol, bufuralol, perbutolol, popindolol, alprenolol, carbedilol, debrisoquin, indolamine, guanoxan, urapidil, nisergolin, risperidone, thioridazine, perphenazine, clozapine, trifluoperol, fluphenazine, chlorpromazine, haloperidol, clomipramine, nortriptyline, amitriptyline, imipramine, trimipramine, desipramine, zolpidem, brofalomine, amiframine, paroxetine, fluoxetine, maprotiline, banrafaxin, fluvoxamin, trazadone, tomoxetin, dihydrocodeine, oxycodone, codeine,

tramadol, dextromethorphan, femformine, perhexelin, chlomiopran, quinidine, cimetidine, ondasteron, etc., are drugs that are metabolized by CYP2D6 and drugs that inhibit CYP2D6. [Translator's note: * indicates transliteration of phonetic characters]

Anfentanyl*, fentanyl, sulfentanyl, cocaine, dihydrocodeine, oxycodone, tramadol, erythromycin, clarithromycin, troleandomycin, azithromycin, itraconazole, ketoconazole, dapson, midazolam, triazolam, alprazolam, diazepam, zolpidem, felodipine, nifedipine, nitrendipine, amlodipine, isradipine, nicardipine, nimodipine, nisoldipine, nildipine, bepridil, diltiazem, verapamil, astemizole, terfenadine, loratidine, cyclosporine, tacrolimus, rapamycin, amiodarone, disopyramide, lidocaine, propafenone, quinidine, imipramine, amitriptyline, clomipramine, nafazodone, sertraline, trazodone, haloperidol, pimozide, carbamazepine, ethosuximide, trimethadione, simvastatin, lovastatin, fluvastatin, atorvastatin, etoposide, ifosfamide, paclitaxel, tamoxifen, taxol, vinblastine, vincristine, indinavir, ritonavir, saquinavir, testosterone, prednisolone, methylprednisolone, dexamethasone, proguanil, warfarin, finasteride, flutamide, ondasteron, zatosetron, cisapride, cortisol, zonisamide, desmethyldiazepam, conivaptan*, etc., are drugs that are metabolized by CYP3A4 and drugs that inhibit CYP3A4 (Sogo Rinsho, 48(6), 1427-1431, 1999/ Seishinka Chiryogaku, 14(9), 951-960, 1999). [Translator's note: * indicates transliteration of phonetic characters]

Inhibition of metabolism resulting in elevation of blood concentration of midazolam and terfenadine, cyclosporine, etc., by erythromycin, methyl prednisolone by ketoconazole, and lovastatin by itraconazole are examples of drugs metabolized by CYP3A4 whose metabolism is inhibited by concomitant use.

Moreover, there are cases where foods that are metabolized by the same species of CYP as drugs compete for the same metabolizing enzymes to inhibit in some way the metabolism of these drugs. Moreover, there are also foods that inhibit a specific molecular species of CYP. For instance, various components contained in grapefruit juice inhibit CYP3A4 and therefore, interaction resulting in elevated blood concentrations of the drugs is seen when cyclosporine and tacrolimus, midazolam, triazolam, terfenadine, etc., which are metabolized by CYP3A4, are taken with grapefruit juice.

On the other hand, it is known that there are drugs that induce drug-metabolizing enzymes. For instance, rifampicin induces CYP3A4, CYP2C9 and CYP2C19 to promote metabolism of nifedipine, warfarin, diazepam, cyclosporine, disopyramide, torbutamide, ethinyl estradiol, etc., and reduce blood concentrations.

(b) Interaction in terms of drug absorption

The route of absorption of drugs is also by the skin or oral mucosa, etc., but the main route of absorption is by the digestive tract.

Changes in gastric pH due to the effect of other drugs used concomitantly changes solubility of drugs and controls or promotes absorption from the digestive tract. For instance, gastric pH rises to 3 to 5 with administration of cimetidine during concomitant use of cimetidine and ketoconazole and as a result, there is a reduction in solubility of ketoconazole and absorption via the digestive tract is inhibited, leading to a reduction in the blood concentration.

There are cases where when a drug is actively absorbed with concomitant drugs via the same carriers on the epithelial cells of the small intestines, absorption of the concomitant drugs is inhibited by this drug. For instance, it is reported that there is a reduction by approximately half in the cefadroxil plasma concentration when cefadroxil, a betalactam antibiotic, is concomitantly administered with cefalexine. This reduction in the blood concentration is apparently due to inhibition as a result of competition for the carrier by the two drugs.

(c) Interaction in terms of drug distribution

Drugs that have been absorbed via the digestive tract or have moved to the blood from the site of administration are distributed to blood cells at a specific ratio, or bind with proteins in plasma. The free fraction of the drug is distributed to each tissue to realize pharmacological action and therefore, when drug bound to protein is expelled from this binding site and interaction occurs so that the concentration of the free fraction of the drug rises, this pharmacological effect is enhanced. For instance, warfarin, torbutamide, etc., are released from the protein binding site, resulting in a rise in the concentration of the free fraction of the drug, when they are concomitantly used with aspirin, etc.

Moreover, P glycoproteins are found in the cells of the mucosa of the small intestines, cells of the uriniferous tubules, and endothelial cells of the capillaries of the brain, and they have the mechanism of transporting many drugs to outside the cells. When a drug that inhibits P glycoprotein is concomitantly used with a drug that is transported via P glycoprotein, there are cases where secretion of drugs into the intestines, transporting drugs out of the brain, and excretion in urine are inhibited. Vinblastin, vincristin, doxorubicin, etoposide, taxol, adriamycin, dexamethasone, hydrocortisone, verapamil, diltiazem, nifedipine, nicardipine, cyclosporin, tacrolimus, acebutolol, metoprolol, nadolol, timolol, prostaglandin, rodamine 123, digoxin, colchicine, dideoxyforskolin, etc., are drugs that are transported out by P glycoproteins. Etoposide, hydrocortisone, progesterone, testosterone, verapamil, diltiazem, nifedipine, felodipine, nitrendipine, nicardipine, cyclosporine, tacrolimus, amiodarone, lidocaine, quinidine, itraconazole, ketoconazole, erythromycin, tamoxifen, terfenadine, clorpromazine, seldiprolol, diprofloxacin, spironolactone are drugs that inhibit P glycoproteins ("Clinical Pharmacokinetics, Revised Version 2," Chapter II. Absorption of drugs from site of administration, page 19, Ryuichi Kato, author, Nankodo Publishers).

(d) Interaction in terms of excretion of drugs.

Drugs that have entered the body are excreted into the urine by the kidneys and are secreted and re-absorbed in the uriniferous tubules. Anionic carriers and cationic carriers participate in secretion from the uriniferous tubules. There is a possibility that drugs that use the same carrier will interact with one another. Probenecid, diodrast, acetazolamide, etc., are drugs that inhibit secretion via anionic carriers. Quinine, methyl nicotinamide, trazolin *transliteration*, tetramethyl ammonium, etc., are drugs that inhibit secretion via cationic carriers.

On the other hand, when re-absorption from the uriniferous tubules is inhibited, there is an increase in the amount excreted in urine and this lowers the blood

concentration. For instance, re-absorption of chlorpropamide from the uriniferous tubules is inhibited by concomitant use with sodium bicarbonate.

A drug delivery system is defined as technology with which fate of drug molecules during the course of drug release, absorption, distribution, metabolism, and excretion is precisely controlled in terms of time and space. Conventional drug delivery systems are used in order to selectively introduce drugs to the site where its effects will be manifested based on the desired concentration-time pattern and thereby obtain the best clinical results. Examples are targeting technology for increasing the therapeutic results of anticancer drugs and steroids at the targeted site while averting adverse reactions outside the targeted site and controlled release technology for reducing the number of administration time of hypotensive agent in 1 day or for avoiding adverse reactions. The use of the drug delivery system of the present invention is in no way intended to alleviate the adverse reactions involved with the drug itself, and it clearly is different from the use of conventional drug delivery systems in that its purpose is to avert undesirable drug interactions between the drug in question and concomitant drugs.

Of the drug delivery systems, technology for controlling release of drugs in particular is used in the present invention. Controlling the release of drugs is generally classified as (1) controlling the release time and (2) controlling the site of release, but there are also cases where the site of release is restricted as a result of controlling the release time and when the release time is delayed as a result of controlling the site of release. Moreover, there are cases in which there is merely a difference in which one of these is mainly controlled.

By means of the present invention, drug interaction between a drug and concomitant drugs is averted by either control by prolonging the drug release time by a certain time period or by controlling release of a drug specifically to a certain site in the digestive tract and as a result, staggering the time at which the drugs will reach the route of absorption, distribution, metabolism or excretion over which the drug competes with concomitant drugs. Consequently, the drug delivery system of the present invention includes cases where release of multiple drugs that are being used concomitantly is controlled, in addition to the case where release of only 1 drug is controlled.

Of the drug delivery systems of the present invention, timed-release control technology and technology for controlling release in the lower digestive tract are particularly effective and will be described below. However, the drug delivery system of the present invention is not particularly limited to these as long as the above-mentioned aversion of drug interaction can be achieved.

(1) Timed-release control technology

Timed-release control is technology with which the time until a drug begins to be released after it has been taken is prolonged for a certain time. This has the mechanism of initiating release of the drug in the preparation by extending the time when it comes into contact with the water content of the digestive tract and in further detail, technology of the following types have been developed (Gekkan Yakuji, 41(6), 35-38, 1999/Igaku no Ayumi, 178(8), 441-444, 1996).

① Insoluble membrane bursting-type

These are preparations where the drug and swelling agent are coated with a membrane that is insoluble in water. The water content penetrates the insoluble membrane to reach the inside, the inside swells, and the insoluble membrane at the surface bursts under pressure so that the drugs inside are exposed to outside liquid. The time until the water permeates and the inside swells so that the membrane ruptures determines the time when drug release begins. Examples are the TES (time-controlled explosion system) of Fujisawa Yakuhin Co., Ltd. (Pharm. Tech. Japan, 4, 1415-1422, 1988) and the prolonged release tablets of Tanabe Seiyaku (Chem. Pharm. Bull, 11, 3036-3041, 1992), whereby a core tablet made of swelling disintegrator is compressed into a tablet with a substance with low water permeability.

② Cap breakaway-type

This is an insoluble capsule filled with drug having a stopper made from a hydrophilic polymer. When water swells the hydrophilic plug and the cap can no longer remain in the opening in the capsule and flips off, the drug inside the capsule comes into contact with outside liquid and is released. The time until the cap flips off determines the time for which release of the drug is prolonged. The Pulsincap of Scherer DDS (Pharm. J., 247, 138, 1991), etc., are given.

③ Membrane permeation increasing-type

The preparation is drug and organic acid inside a resin layer comprising cationic groups. The water content penetrates the resin layer, the organic acid inside is dissolved, and the acid and cationic groups of the resin interact, resulting in an increase in penetrability of the resin and release of the drug. The granules of Tanabe Seiyaku (Maku 19, 392-399, 1994) comprising Eudragit RS as the outer layer and organic acid and drug as the inner layer, etc., are given.

④ Hydrogel layer dissolving-type

This is a preparation of drug encapsulated by hydrophilic polymer. The water content soaks into the hydrophilic polymer, the polymer gel is gradually dissolved, and the drug inside comes into contact with outside liquid and is released. The gel shape and gel dissolution determine the time for which release of the drug will be prolonged. The chronotropic DDS coated with a hydroxypropyl methyl cellulose layer of Milano University (Eur. J. Pharm. Biopharm, 40, 246-250, 1994) and tablets of Kumamoto University (Chem. Pharm. Bull., 43, 311-314, 1995) whereby hydroxyethyl cellulose is compressed into the core tablet containing drug are given as examples.

Furthermore, the applicant developed as an improved form a tablet with a core, which is obtained by compression molding a hydrophilic base and a hydrogel-forming polymer substance together with a core tablet containing drug. This preparation can be used as a drug delivery system for averting undesirable interaction between multiple drugs metabolized by the drug-metabolizing enzyme CYP3A4. This preparation preferably is a combination of a dissolving filler mixed in the core tablet containing drug in order to completely dissolve or suspend the drug before drug release begins. Malic acid, citric acid, polyethylene glycol, sucrose, etc., are given as examples of the

dissolving filler. A base that has a solubility of no more than 4 ml as the volume of water needed to dissolve 1 g of the base is preferred as the hydrophilic base, and water-soluble polymers such as polyethylene glycol, polyvinyl pyrrolidone, etc., sugar alcohols, such as D-sorbitol, xylitol, etc., saccharides, such as sucrose, maltose, lactulose, D-fructose, dextran, glucose, etc., surfactants, such as polyoxyethylene hydrogenated castor oil, polyoxyethylene polyoxypropylene glycol, polyoxyethylene sorbitan higher fatty acid esters, etc., salts, such as sodium chloride, magnesium chloride, etc., organic acids, such as citric acid, tartaric acid, etc., amino acids, such as glycine, β -alanine, lysine hydrochloride, etc., aminosaccharides, such as meglumine, etc., are given as examples. Polyethylene oxide, hydroxypropylmethyl cellulose, carboxymethyl cellulose sodium, hydroxyethyl cellulose, carboxyvinyl polymer, etc., are given as the hydrogel-forming polymer, and those with a high viscosity at the time of gelling or with a high viscosity-average molecular weight are preferred.

(2) Technology for controlling release in the lower digestive tract

Controlling release in the lower digestive tract is technology for controlling initial release of the drug until the preparation has reached the lower digestive tract, such as the ileum and/or colon, etc., after being taken. It has the mechanism of releasing the drug in the environment of the lower digestive tract.

The ileum and colon have more bacteria than the stomach or upper small intestine and therefore, by coating the drug with a polymer that is decomposed by bacterial enzymes, the drug is not released in the stomach or upper small intestines. The polymer at the preparation surface is decomposed and dissolved and the drug is released after reaching the ileum and/or colon. Systems whereby azo aromatic polymers are decomposed by the azo reductase of intestinal flora of the University of Ohio (Science 233, 1081, 1986) and the University of Utah (Pharmaceutical Research, 9(12), 1540-1545, 1992), systems whereby polysaccharides are decomposed by the β -galactosidase of intestinal flora of Freiburg University (Pharmaceutical Research 10(10), S218, 1993), and systems of decomposition by chitosanase using chitosan of Teikoku Seikayu (Japanese Patent No. Hei 4(1992)-217924) are given. A system that uses a lectin-type substance present in the large intestines of the University of Utah (Proc. Int. Symp. Control. Rel. Bioact. Mat., 17, 130-131, 1990) is also reported.

Furthermore, there is also the system of the applicants (International Disclosure No. 95/28963) whereby organic acid is generated using intestinal bacteria and as a result, the film covering the drug is dissolved by said organic acid without affecting pH of the nearby cecum and the drug is specifically released to a site in the colon. In concrete terms, it is a system for specific release of drug in the colon of the digestive tract consisting of drug that is coated with a polymer that is dissolved by an organic acid and a saccharide that quickly generates an organic acid as a result of reaction with intestinal flora in the lower digestive tract.

The drug preparation for averting drug interaction of the present invention can be prepared by conventional methods as an oral solid preparation, an oral liquid preparation, or an injection using the above-mentioned timed-release technology and/or technology for controlling the site of release and an organic or inorganic carriers, filler, and other

additives appropriate for oral or non-oral administration. The drug preparation of the present invention is preferably an oral drug preparation.

A system for averting drug interaction that uses the drug delivery system of the present invention will now be explained based on the type of drug interaction.

(a) System for averting interaction in terms of drug metabolism

In general, when multiple drugs that are metabolized by a drug-metabolizing enzyme of the same molecular species compete for a metabolizing enzyme in the liver, metabolism of the drug that has inferior affinity for the metabolizing enzyme is inhibited and interaction in the form of a rise in the blood concentration and prolonged blood half life is seen. In addition, when a drug that is metabolized by a certain drug-metabolizing enzyme and a drug that interferes with the same metabolizing enzyme are both present in the liver, metabolism is inhibited and interaction in the form of a rise in the blood concentration and prolonged blood half life is seen. Consequently, competition with concomitant drugs over a drug-metabolizing enzyme can be averted by controlling the release time so that a drug will reach the drug-metabolizing enzyme in the liver a specific time after a concomitant drug has been absorbed. Moreover, competition over a drug-metabolizing enzyme can be averted by releasing a drug specifically in the lower digestive tract and thereby staggering the time when concomitant drugs reach the liver.

In addition, CYP3A4 accounts for more than half of drug metabolism by CYP and as much as 80% of the amount distributed to the liver is also distributed to upper small intestines consisting of the duodenum and jejunum. Therefore, when a drug metabolized by CYP3A4 is orally administered, it is metabolized at the epithelium of the small intestines before it is absorbed from the digestive tract. Consequently, competition over CYP3A4 in the upper small intestines can be averted by (1) delaying the drug release time using timed-release control technology, which should avert coexistence of at the site of metabolism of concomitant drugs (epithelium of the small intestines and liver) or (2) by releasing the drug in the ileum and colon in which little CYP3A4 is distributed using technology for controlling release specifically in the lower digestive tract.

For instance, inhibition of midazolam metabolism due to competition with conivaptan *transliteration* and the rise in the blood concentration that accompanies the same can be averted by administration with a timed-release preparation with which release of the conivaptan in the digestive tract is delayed by as much as 2 hours, as shown in the examples and test examples given later.

(b) System for averting interaction in terms of drug absorption

Interaction involving absorption of drugs occurs mainly in the digestive tract with oral administration and is the result of an effect on solubility and permeability of the intestinal epithelium due to a change in gastric pH. In concrete terms, drug interaction can be averted by (1) timed-release control whereby a drug reaches the site of the digestive tract in question once absorption of concomitant drugs from the digestive tract has been completed or (2) by technology for controlling the site of release site whereby the site in the digestive tract at which concomitant drugs are absorbed is avoided.

For instance, a reduction in the plasma concentration of cefadroxil due to competition between cefadroxil and cephalixin over a carrier can be averted by administration with a timed-release preparation with which release of the cephalixin is delayed by as much as 3 hours.

(c) System for averting interaction in terms of drug distribution

Interaction involving drug distribution usually occurs with competition over a protein in the blood. Drug interaction in the blood can be averted by timed-release control or releasing a drug specifically in the lower digestive tract so that it reaches the blood after the blood concentration of concomitant drugs has dropped to a certain point.

For instance, inhibition of binding of acetohexamide with blood proteins induced by aspirin and a rise in the free acetohexamide concentration of the blood and hypoglycemic symptoms that accompany the same can be averted by controlling liberation of acetohexamide from blood proteins as a result of administration of aspirin with a timed-release preparation with which release in the digestive tract is delayed by as much as 4 hours after oral administration.

(d) System for averting interaction in terms of drug excretion

Interaction involving drug excretion often occurs due to competition over a carrier in the uriniferous tubules. Interaction in the uriniferous tubules can be averted by timed-release control or release of a drug specifically to the lower digestive tract so that a drug reaches the kidneys once excretion of concomitant drugs from the uriniferous tubules has been completed for the most part.

For instance, a reduction in renal excretion as a result of inhibition of secretion of procainamide via the uriniferous tubules induced by competition from cimetidine and an increase in the blood concentration that accompanies the same can be averted by oral administration with a timed-release preparation with which release of procainamide in the digestive tract is delayed by as much as 4 hours so that inhibition attributed to competition over secretion from the uriniferous tubules is controlled.

The system for averting drug interaction of the present invention can include other technology as long as the *in vivo* release time and/or release site of 1 or multiple drugs is controlled.

Brief Description of the Drawings

Figure 1 shows the results of dissolution tests of conivaptan timed-release preparation.

Figure 2 shows time course of the blood concentration of midazolam when conivaptan (aqueous solution or timed-release preparation) and midazolam were simultaneously administered orally to dogs.

Best Mode for Carrying Out the Invention

A drug delivery system with which there is timed-release control of conivaptan *transliteration* in order to avert drug interaction due to concomitant use of conivaptan and midazolam, which are metabolized by the metabolizing enzyme CYP3A4, will be

described with examples and test examples. Midazolam is marked under the brand names of Dormicum, Hypnovel, Versed, etc. Conivaptan is easily obtained by or in accordance with the production method described in International Kokai Patent N. 95/03305.

However, the present invention is not limited to these examples, etc.

Example 1: Conivaptan timed-release preparation

After dissolving 1 part by weight conivaptan hydrochloride, 3 parts by weight HPMC2910, and 0.5 parts by weight polysorbate 80 in 85.5 parts by weight of a dichloromethane-methanol mixed solution (8:2), a solid dispersion was prepared by spray drying. Six parts by weight malic acid were added to 9 parts by weight of the solid dispersion and mixed with a mortar and pestle. Core of 150 mg/tablet with a diameter of 6.5 mm were obtained under a tableting pressure of 500 kg/punch using an oil press. At the same time, 62.5 mg polyethylene oxide (Polyox[®] WSR303) and 187.5 mg Macrogol 6000 were mixed with a mortar and pestle as the outer layer. The core tablet was placed in the center of the outer layer and compression coated tablets of the present invention of 400 mg (20 mg conivaptan)/tablet with a diameter of 9.5 mm were made under a tableting pressure of 1,000 kg/punch using an oil press.

Test Example 1: Dissolution tests

Dissolution tests were conducted on the preparation in Example 1. The tests were conducted by the Second Dissolution Testing Method (Paddle Method) of the Pharmacopoeia of Japan (paddle rotation: 200 rpm) using 500 ml of 1st fluid of the Disintegration Testing Method of the Pharmacopoeia of Japan as the dissolution medium. Sampling was performed each hour and the conivaptan in the sampled solution was determined by the UV method.

(Results)

The results of the dissolution test are shown in Figure 1. As is clear from the figure, it was confirmed that release of conivaptan started approximately 4 hours later with the timed-release preparation of Example 1.

Test Example 2

(Preparation of Sample Solution)

(1) Aqueous solution for oral administration containing midazolam: After preparing commercial midazolam injectable liquid (brand name: Dormicum[®] injection) to a concentration of 0.2 mg/ml with aqueous hydrochloric acid solution (pH of 3), HPMC2910 was added at 3-times the amount of midazolam to obtain a liquid for oral administration.

(2) Aqueous solution for oral administration containing conivaptan: Conivaptan hydrochloride was dissolved to a concentration of 0.5 mg/ml with an aqueous hydrochloric acid solution (pH of 3) to obtain a liquid for oral administration.

(Experiment 1)

Male beagle dogs (n = 6) that had been fasted for approximately 20 hours were orally administered the aqueous solution for oral administration containing midazolam using a catheter for oral administration (4 mg/dog). After administration, blood was collected from the veins of the front legs and the plasma concentration of midazolam was determined by the HPLC/UV method over time.

(Experiment 2)

Male beagle dogs (n = 6) that had been fasted for approximately 20 hours were orally administered the aqueous solution for oral administration containing conivaptan (10 mg/dog). Thirty minutes after administration the aqueous solution for oral administration containing midazolam was orally administered using a catheter for oral administration (4 mg/dog). After midazolam administration, blood was collected from the veins of the front legs and the plasma concentration of midazolam was determined by the HPLC/UV method over time.

(Experiment 3)

Male beagle dogs (n = 6) that had been fasted for approximately 20 hours were orally administered the timed-release preparation of conivaptan of Example 1 (20 mg/dog) with 30 ml of water. Thirty minutes after administration an aqueous solution for oral administration containing midazolam (4 mg/dog) was orally administered using a catheter for oral administration. After midazolam administration, blood was collected from the veins of the front legs and the plasma concentration of midazolam was determined by the HPLC/UV method over time.

(Results)

The results are shown in Figure 2 and the following table.

Table 1. AUC of plasma concentration of midazolam

	AUC (ng · h/ml)
Experiment 1 (midazolam singular administration)	9.0 ± 6.0
Experiment 2 (" + aqueous conivaptan solution)	21.2 ± 8.5*
Experiment 3 (" + conivaptan timed-release preparation)	10.9 ± 7.3

*:p < 0.05 (to Experiment 1)

As is clear from the results from Experiment 1 and Experiment 2, when the aqueous solution for oral administration containing conivaptan was concomitantly used by oral administration before oral administration of midazolam, there was a significant rise in the blood concentration of midazolam when compared to midazolam singular oral administration, or there were significant changes, such as the area under concentration curve (AUC) being at least twice as large as that with midazolam singular administration (Figure 2 and Table 1).

The reason for this appears to be that conivaptan, which adopts the same route of metabolism by CYP3A4, inhibits metabolism of midazolam in the small intestines and as a result, increases the blood concentration of midazolam and the AUC.

On the other hand, as is clear from Experiment 1 and Experiment 3, approximately the same results as with midazolam singular administration were seen in terms of changes in the blood concentration of midazolam and the AUC when the timed-release preparation of Example 1 was concomitantly used before midazolam oral administration (Figure 2 and Table 1). It appears from this finding that because conivaptan is released after the midazolam has been metabolized by CYP3A4 with the timed-release preparation of the present invention, the conivaptan does not inhibit metabolism of CYP3A4 in the small intestine or liver and therefore, there is no effect on the blood concentration or AUC of midazolam. Moreover, it was confirmed that the blood concentration and AUC were the pharmacological therapeutic or preventive levels of conivaptan once the midazolam had cleared from the blood.

Based on the above-mentioned, it was confirmed that the undesirable effects on the blood concentration of concomitant drugs by drugs when drugs and concomitant drugs are metabolized by the drug-metabolizing enzyme CYP3A4 can be averted with the drug delivery system that uses timed-release control of the present invention.

Industrial Applicability

Undesirable pharmacokinetic drug interaction that occurs with concomitant use of multiple drugs can be averted using the system for averting drug interaction of the present invention. Consequently, novel treatment by a combination of drugs that could not be concomitantly used in the past is possible. Furthermore, drug products can be developed and novel drug products can be presented from drugs that were impossible to develop in the past because of drug interaction when used concomitantly with other drugs, regardless of their excellent pharmacological effects and lack of problems with adverse reactions.

In addition, it is possible to avert undesirable pharmacokinetic adverse reactions when a drug has been taken with a specific food with the system for averting drug interaction of the present invention. Consequently, patient compliance will be improved because the precautions for use explained to the patient by a pharmacist will be reduced.

Claims

1. A system for averting undesirable pharmacokinetic drug interaction between multiple drugs, which consists of controlling the *in vivo* release time and/or release site of 1 or multiple drugs.
2. A system for averting undesirable drug interaction between multiple drugs that use the same route in terms of *in vivo* drug absorption, distribution, metabolism or excretion in humans, which consists of controlling the *in vivo* release time and/or release site of 1 or multiple drugs.
3. A system for averting undesirable drug interaction between multiple drugs that are metabolized by the same molecular species of drug-metabolizing enzyme in humans, or between drugs and other drugs that inhibit the molecular species of drug-metabolizing enzymes that metabolize the same drugs, which consists of timed-release control or controlling the site of release in the digestive tract of 1 drug.
4. A system for averting undesirable drug interaction between multiple drugs metabolized by the drug-metabolizing enzyme CYP3A4, or between drugs that are metabolized by CYP3A4 and other drugs that inhibit CYP3A4, which consists of timed-release control or controlling release specifically to the lower digestive tract of 1 drug.
5. The use of a drug delivery system whereby the *in vivo* release time and/or release site of 1 or multiple drugs is controlled as a means for averting undesirable pharmacokinetic drug interaction between multiple drugs.
6. A method of averting undesirable pharmacokinetic drug interaction between multiple drugs by using a drug delivery system whereby the *in vivo* release time and/or release site of 1 or multiple drugs is controlled.
7. A drug preparation for averting undesirable pharmacokinetic drug interaction between drugs and concomitant drugs, with which the *in vivo* release time and/or release site of the drugs can be controlled.
8. A drug preparation according to Claim 7 for averting undesirable drug interaction between drugs and concomitant drugs that use the same route in terms of *in vivo* drug absorption, distribution, metabolism or excretion in humans, with which release time and/or release site of the drug can be controlled.
9. A drug preparation according to Claim 8 for averting undesirable drug interaction with the *in vivo* kinetics of concomitant drugs by drugs that inhibit *in vivo* metabolism by a drug-metabolizing enzyme of concomitant drugs in humans, with which the timed-release control or control of the release site in the digestive tract of a drug can be controlled.
10. A drug preparation according to Claim 9 for averting undesirable effects on the blood concentration of concomitant drugs by drugs that inhibit *in vivo* metabolism of concomitant drugs by CYP3A4 in humans, with which timed-release control or control of release specifically to the lower digestive tract is possible.

11. A drug preparation according to Claim 10, whereby the drug and concomitant drugs are a combination selected from anfentanyl, fentanyl, sulfentanyl, cocaine, dihydrocodeine, oxycodone, tramadol, erythromycin, clarithromycin, troleandomycin, azithromycin, itraconazole, ketoconazole, dapson, midazolam, triazolam, alprazolam, diazepam, zolpidem, felodipine, nifedipine, nitrendipine, amlodipine, isradipine, nifedipine, nimodipine, nisoldipine, nifedipine, bepridil, diltiazem, verapamil, astemizole, terfenadine, loratadine, cyclosporine, tacrolimus, rapamycin, amiodarone, disopyramide, lidocaine, propafenone, quinidine, imipramine, amitriptyline, clomipramine, nafazodone, sertraline, trazodone, haloperidol, pimozide, carbamazepine, ethosuximide, trimethadione, simvastatin, lovastatin, fluvastatin, atorvastatin, etoposide, ifosfamide, paclitaxel, tamoxifen, taxol, vinblastine, vincristine, indinavir, ritonavir, saquinavir, testosterone, prednisolone, methylprednisolone, dexamethasone, proguanil, warfarin, finasteride, flutamide, ondansetron, zolasetron, cisapride, cortisol, zonisamide, desmethyldiazepam, and conivaptan.
12. The use of a drug preparation with which the *in vivo* release time and/or release site of drugs can be controlled in order to avert adverse pharmacokinetic drug interaction between drugs and concomitant drugs.
13. A method for averting undesirable pharmacokinetic drug interactions between drugs and concomitant drugs by using a drug preparation with which the release time and/or release site of the drug can be controlled.
14. A system for averting undesirable pharmacokinetic interaction between drugs and food, whereby the *in vivo* release time and/or release site of the drug is controlled.
15. A drug preparation for averting undesirable pharmacokinetic interaction between drugs and food, with which the *in vivo* release time and/or release site of a drug can be controlled.

Abstract

The present invention is a system for averting undesirable pharmacokinetic drug interaction between multiple drugs, which consists of controlling the *in vivo* release time and/or release site of 1 or multiple drugs. Moreover, the present invention is a drug preparation for averting undesirable pharmacokinetic drug interaction between drugs and concomitant drugs, with which the *in vivo* release time and/or release site of drugs can be controlled.

Translator's note: Followings are transliteration of phonetic characters

N-propylazimalin, nisergolin, trifluoperiol, brofalomin, amiframine, banrafaxin, tomoxetin, anfentanyl, conivaptan, trazolin